Attorney Docket No. 3523 P 002

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re U.S. Patent Application of:
Wilhelm SCHWAEBLE & Robert Braidwood SIM

From: PCT/GB97/03275 28 November 1997
British Appln. No. 9624731.7 28 November 1996

For: COMPLEMENT INHIBITOR

REQUEST FOR FILING A CONTINUATION OF AN INTERNATIONAL APPLICATION

ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

ATTN: BOX PATENT APPLICATION

Sir:

This is a request for filing a continuation application under 37 C.F.R. 1.53(b), of pending prior International Application No. PCT/GB97/03275, filed 28 November 1997 (claiming priority from British Appln. No. 9624731.7, filed 28 November 1996), titled COMPLEMENT INHIBITOR, which designated the United States.

Enclosed are the specification, claims and Abstract, along with 15 sheets of formal drawings (Figures 1-4).

The filing fee has been calculated as shown below:

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□ First Presentation of Multiple Dependent Claim			x130 =		or	x 260 =	
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Amend the specification by inserting before the first line the sentence: "This Application is a Continuation of International Application No. PCT/GB97/03275, filed 28 November 1997 (claiming priority from British Appln. No. 9624731.7, filed 28 November 1996), now pending (which is hereby incorporated by reference)."

⇨ Priority of foreign Application No.9624731.7 filed 28 November 1996 in Britain is claimed under 35 U.S.C. 119(a)-(d).

⇨ A Preliminary Amendment is enclosed.

We also enclose for completeness:

- PCT application as published (without search report)
- International Search Report
- Notification of Transmittal of International Preliminary Examination Report
- Notification Concerning Submission of Priority Document
- Notice Informing Applicant of Communication of International Application to Designated Offices
- Information Concerning Elected Offices Notified of Their Election
- Notification of Receipt of Demand

Respectfully submitted,

Date: May 21, 1999

By: Monique A. Morneault

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Susan M Franklin

Attorney Docket No. 3523 P 002 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re U.S. Patent Application of:)
Wilhelm SCHWAEBLE & Robert SIM)
)
From: PCT/GB97/03275 28 November 1997)
British Appln. No. 9624731.7 28 November 1996)
)
For: COMPLEMENT INHIBITOR)

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

ATTN: BOX PATENT APPLICATION

Please amend the above-identified application as follows:

IN THE CLAIMS:

Claim 3, delete the phrase "either one of claims 1 or 2" and insert -- claim 1 -- .

Claim 7, delete the phrase "either one of claims 1 or 2" and insert -- claim 1 -- .

Claim 9, delete the phrase "any one of claims 1-8" and insert -- claim 1 -- .

Claim 11, delete the phrase "any one of the preceding claims" and insert -- claim 1 -- .

Claim 12, late line, delete the phrase "any one of claims 1-10" and insert -- claim 1 -- .

Claim 13, last line, delete the phrase "any one of claims 1-10" and insert -- claim 1 -- .

Claim 16, last line, delete the phrase "any one of claims 1-10" and insert -- claim 1 -- .

The above amendments are being submitted to place the claims in proper format. No new matter is being added through these amendments. Applicant respectfully requests entry of the above amendments.

Respectfully submitted,

Date: May 21, 1999

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Susan M Franklin

In re CONTINUATION application of: UNIVERSITY OF LEICESTER
Inventors: Wilhelm SCHWAEBLE and Robert Braidwood SIM

For: COMPLEMENT INHIBITOR

Our Docket No. 3523 P 002 (M96/0591/US)

THIS APPLICATION CLAIMS PRIORITY FROM PCT/GB97/03275 (FILED 28 NOVEMBER 1997) AND BRITISH APPLN. NO. 9624731.7 (FILED 28 NOVEMBER 1996)

ENCLOSED: POSTCARD

REQUEST FOR FILING A CONTINUATION OF AN INTERNATIONAL APPLICATION

34-PAGE PATENT APPLICATION

2-PAGE PRELIMINARY AMENDMENT

15 SHEETS OF FORMAL DRAWINGS (FIGURES 1-4)

PCT application as published (without search report)
International Search Report
Notification of Transmittal of International Preliminary Examination Report
Notification Concerning Submission of Priority Document
Notice Informing Applicant of Communication of International Application to Designated Offices
Information Concerning Elected Offices Notified of Their Election
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I HEREBY CERTIFY THAT THIS PAPER AND THE ABOVE DOCUMENTS ARE BEING DEPOSITED WITH THE U.S. POSTAL SERVICE AS EXPRESS MAIL IN AN ENVELOPE ADDRESSED TO BOX PATENT APPLICATIONS, ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, DC 20231, ON May 21, 1999 UNDER EXPRESS MAIL NO. EL237761323US.

Susan McFranklin

PLEASE ADDRESS ALL FUTURE COMMUNICATIONS TO:

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Complement Inhibitor

The present invention concerns regulation of complement activation, in particular the fluid phase regulation of complement activation.

The complement system (see McAleer, M.A. and Sim, R.B. in Activators and Inhibitors of Complement, Kluwer Academic Publishers, Dordrecht, ed R.B. Sim, 1993, p. 1-15; Reid, K.B.M. and Law, A., 1988, Complement, IRL Press, Oxford) is concerned with host defence against infection - upon activation of the system a catalytic set of reactions and interactions occur resulting in the targeting of the activating cell, organism or particle for destruction. Due to the destructive nature of the system it has the potential to cause severe damage to a host system if incorrectly triggered (Davis, A.E., 1988, Ann. Rev. Immunol., 6: 595-628; Frank, M.M., 1993, In: Complement in Health and Disease, 2nd Edition, Whaley, K. *et al.* eds., Kluwer Academic Publishers, Dordrecht, p. 229) and if its activity is diminished then it has the potential to leave the host open to attack from infecting pathogens.

This is particularly the case with patients suffering from Factor H (FH) deficiency which leads to an uncontrolled activation of the complement system resulting in a depletion of serum complement. Factor H deficient patients are susceptible to recurrent bacterial infection (particularly meningitis) and may not be able to clear immune complexes efficiently from circulation, resulting in glomerulonephritis.

Factor H is an important complement regulator which controls activation by its virtue to bind to native and complexed C3b and to serve as a cofactor in the Factor I mediated conversion of C3b to haemolytically inactive iC3b (Whaley, K. and Ruddy, S., 1976, J. Exp. Med., 144: 1147). It thereby acts as an antagonist to factor B and holds in check the alternative pathway activation, a positive feedback loop in which C3b

complexes with factor B, after which the serine protease factor D activates factor B by proteolysis, to form the alternative pathway C3 convertase, C3bBb. Factor H has a further important regulatory function as it can accelerate the decay of the C3 convertase by displacing Bb from the complex (Whaley, K. and Ruddy, S., 1976, Science, 193: 1011). Absence of factor H results in uncontrolled turnover of the alternative pathway. Because C3b is an integral component of the C5 convertases of both classical and alternative pathways, the binding of factor H to C3b also regulates C5 convertase activity (Whaley, K. and Ruddy, S., 1976, Science, 193: 1011). Thus factor H plays a key role in controlling the alternative pathway C3 convertase activity and also the activities of the C5 convertases of both classical and alternative pathways.

No complement regulatory activity has as yet been ascribed to the recently characterized variant factor H related serum glycoproteins of 39/43 kDa and 24/29 kDa (Timmann, C. *et al.*, 1991, J. Immunol., 146:1265; Estaller, C. *et al.*, 1991, J. Immunol., 146: 3190; Schwaeble, W. *et al.*, 1991, Eur J. Biochem., 198: 399 - 404; Skerka, C. *et al.*, 1991, J. Biol. Chem., 266: 12015; Zipfel, P.F. and Skerka, C., 1994, Immunology Today, 15: 121). These factor H related mRNAs are exclusively expressed in the liver (Schwaeble, W. *et al.*, 1991, Immunobiol., 182:307) and encoded by at least two different factor H related genes (Estaller, C. *et al.*, 1991, J. Immunol., 146: 3190; Hourcade, D. *et al.*, 1991, Abstr. XIVth Int. Complement Workshop, Complement Inflamm., 8: 163; Zipfel, P.F. and Skerka, C., 1994, Immunology Today, 15: 121).

Factor H comprises a number of independently folded domains (CCP modules or short consensus repeats - SCRs) of approximately 60 amino acid (aa) residues with a framework of highly conserved residues involving 4 cysteine, 1 tryptophane and 2 proline residues. In human serum, two different FH glycoproteins of 155 kDa (FHp155) and of 43 kDa (FHp43) are known (Schwaeble. W. *et al.*, 1987, Eur. J. Immunol., 17: 1485; Ripoche, J. *et al.*, 2988, Biochem. J., 249: 593; Schwaeble, W. *et al.*, 1991, Eur. J. Biochem., 198: 399-404; Estaller, C. *et al.*, Eur. J. Immunol., 21:

799) and both forms express cofactor (i.e. complement regulatory) activity in the FI (Factor I) mediated conversion of C3b to iC3b (Misasi, R. *et al.*, 1989, Eur. J. Immunol., 19: 1765 - 1768). See also Whaley, K. and Ruddy, S., 1976, J. Exp. Med. 144: 1147-1163; Whaley, K. and Ruddy, S., 1976, Science, 193: 1011-1013.

According to the present invention there is provided a molecule comprising at least complement control protein (CCP) modules (Reid, K.B.M. *et al.*, 1986, Immunol. Today, 7: 230-234) 1-4 of complement factor H, or a molecule resulting from partial modification thereof or an allelic mutant thereof.

By "partial modification" and "partially modified" is meant, with reference to amino acid sequences a partially modified form of the molecule which retains substantially the properties of the molecule from which it is derived, although it may of course have additional functionality. Partial modification may, for example, be by way of addition, deletion or substitution of amino acid residues. Substitutions may be conserved substitutions. Hence the partially modified molecules may be homologues of the molecules from which they are derived. They may, for example, have at least 40% homology with the molecules from which they are derived. They may for example have at least 50, 60, 70, 80, 90 or 95% homology with the molecules from which they are derived. Similarly nucleotide sequences encoding the molecules or amino acid sequences may be partially modified to code for any such modifications to an amino acid sequence or molecule. Nucleotide sequences may also of course be modified such that they still code for the same amino acid residues but have a different nucleotide sequence.

The molecule may for example comprise CCP modules 1-4, 1-5 or 1-6 of complement factor H, or a molecule resulting from partial modification thereof or an allelic mutant thereof.

The present inventor have found that, surprisingly, truncated recombinant factor H expressed in yeast is approximately 10-100 fold more potent (see Figure 4) than the serum protein FHp155, and that this potency is to be found particularly in constructs representing CCP modules 1-6, CCP modules 1-5, and CCP modules 1-4. For example (Figure 4) at a 100 nM concentration a 30-40 fold increase in efficacy is observed. This specific potency in CCP modules (SCRs) 1-4, 1-5 and 1-6 has not previousl been suggested or disclosed.

The complement factor H may be human complement factor H or it may for example be a different animal complement factor H, for example rat complement factor H.

The molecule may comprise FHp43, or a molecule resulting from partial modification thereof or an allelic mutant thereof.

The molecule may be for use in inhibiting complement activation.

Hence a molecule according to the present invention may have increased complement inhibitory activity compared to that of FHp155, i.e. it may have an enhanced efficacy. A molecule according to the present invention comprises at least CCP modules 1-4 of FHp43. It may for example comprise at least CCP modules 1-4, 1-5 or 1-6 of FHp43.

A molecule comprising human factor H CCP modules 1-4, 1-5 or 1-6 may have the sequence of SEQ ID NO: 9, 10 or 11 respectively. A molecule comprising rat factor H and having CCP modules 1-7 may have the sequence of SEQ ID NO: 14.

The present inventors have found that the C-terminal 180 amino acids of FHp43 may be removed without significant loss of the complement inhibitory function

of FHp43. Hence molecules according to the present invention may have C-terminal deletions of for example about 180 amino acids, when compared to FHp43.

The regulatory activity of these molecules may be used for example in preventing tissue damage due to myocardial infarction, ischemia (for example limb and gut ischemia), infarction of neural tissue, in treating the adult respiratory distress syndrome, rheumatoid arthritis and thermal injuries. The molecules may be used as a fluid phase regulator of complement activity. They may for example be used to improve the biocompatability of artificial membranes by e.g. coating haemofiltration membranes with immobilised FH polypeptides in order to reduce complement activation or by encapsulating xenografts in artificial membranes coated with FH polypeptides. Fusion proteins may be made comprising a FH protein according to the present invention fused to a membrane anchor in order to act as a potent complement regulator on the surface of transfected (or transformed) cells and transgenic animals. Such membrane anchored molecules may be used to reduce xenograft rejection using xenotransplant organs. Spacer residues may be added between the membrane anchor and the FH protein in order to increase or optimise the efficacy of the FH protein (Adams, E.M. *et al.*, 1991, J. Immunol., 147: 3005). Methods of transformation and transfection of cells are well known in the art and where reference is made to transfection, reference is also to transformation and *vice versa*.

Molecules according to the present invention may be modified such that they have an increased half-life in order that they may have a prolonged protective effect upon a patient. Particular molecules may for example comprise dimeric or trimeric forms of molecules according to the present invention. For example a molecule may comprise a trimer of CCP modules 1-4 or a trimer of FHp43.

Also provided according to the present invention is the use of a molecule according to the present invention in the manufacture of a medicament for inhibiting

complement activation. Also provided according to the present invention is a method of manufacture of a medicament for inhibiting complement activation, comprising the use of a molecule according to the present invention.

Also provided according to the present invention is a method of inhibiting complement activation comprising the use of a molecule according to the present invention.

Although human Factor H has previously been clones, researchers have so far failed to clone rat Factor H. The present inventors have now succeeded in isolating and sequencing rat FH 4.3 and FH1.0 mRNA and so according to the present invention there is also provided a nucleotide sequence having the sequence of SEQ ID NO: 1 (Figure 1 - FH4.3) encoding rat FH 4.3 kb mRNA, together with a nucleotide sequence having the sequence of SEQ ID NO: 2 (Figure 1 - FH1.0) encoding rat FH 1.0 kb mRNA. The present invention also extends to partially modified forms of the nucleotide sequences and to polypeptides derived from them and partially modified forms thereof.

FHp155 and FHp43 may be readily isolated and purified (Misasi, R. *et al.*, Eur. J. Immunol., 1989, 19: 1765-1768; Sim, R.B. *et al.*, 1993, Int. Rev. Immunol., 10: 65; Sim, R.B. *et al.*, 1993, Meth. Enzymol., 223: 13 and references therein) and the genes encoding the proteins may be isolated using standard techniques. Standard expression systems, for example MaxBac (Invitrogen) may be used to synthesise the isolated protein (see Sharma, A.K. and Pangburn, M.K., 1994, Gene, 143: 301).

The ability of the molecules of the present invention to inhibit complement activation may be readily shown by activating complement with antigen-antibody complexes (classical pathway) or zymosan (alternative pathway) in the presence of the molecules of the present invention and assaying levels of C3a, C5a and C5b-9

complement components using commercially available reagents (Amersham) and ELISA (enzyme linked immunosorbent assay).

The alternative pathway C3 and C5 convertases ($(C3b)_nBbP$) and classical pathway C5 convertase (C4b2a3b) may be readily prepared from for example rat or human components and the activity of the factor H molecules of the present invention on the formation and stability of each convertase and on C5 activation may be assayed using haemolytic assay systems (Sim *et al.*, 1993, *supra*).

The ability of the molecules of the present invention to inhibit complement activation and limit tissue injury *in vivo* may be determined using for example a model of perfusion injury of ischaemic myocardium (Weisman, H.F *et al.*, 1990, Science, 249: 146) and a model of antibody-dependent experimental allergic encephalomyelitis (Piddlesden, S. *et al.*, 1990, Clin. Exp. Immunol., 83: 245).

The molecules of the present invention may be readily coupled to artificial membranes, for example dialysis membranes, as follows. Using cuprophan-cellulose membranes (Enka-Azko, Wuppertal, Germany), the following steps may be performed:

i) Activation of the membrane:

1,1'-Carbodiimidazole (Kennedy, J.F. and Paterson, M., 1993, Polymer. Intern., 32: 71;

Chlorformic acid-p-nitrophenylester (Vandorne, F. *et al.*, 1991, Makromol. Chem., 192: 773);

Cyanogen bromide (Kennedy, J.F. and Patterson, M., 1993, *supra*)

ii) Coupling of spacers:

Use of aliphatic diamines (e.g. 1,12 Diaminododecane, Kery *et al.*, 1991, Carbohydr. Res., 209: 83);

Use of 6-aminocaproicacid (Burton, S.C., 1991, J. Chromatogr., 587: 271);

Use of aminosubstituted aliphatic thiols (Kery *et al.*, 1991, *supra*)

iii) Coupling of the peptide:

Activation of the N-terminal spacer by thiophosgen;

Activation of a carboxyterminal spacer using alternatively the acid method or the addition of coupling reagents (e.g. DCC or EDC, Royer, G.P. and Anantharmaiah, G.M., 1979, J. Am. Chem. Soc., 101: 3395; Bodanszky, M. and Bodanszky, A., 1984, K. Hafner *et al.*, Hrsg, Bd. 21, Springer-Verlach, Berlin);

Activation of S-terminal spacer by 2,2'-Dithiodipyridine and coupling via cysteine residues.

The effect of uncoated and coated membranes (above) upon complement activation may be readily quantified using C3a, C5a and C5b-9 assays (Chenoweth, D.E., 1987, Contr. Nephrol., 59: 51 and as described above).

According to a further aspect of the invention, there is provided a DNA molecule, which may be in recombinant or isolated form, comprising a sequence encoding a molecule according to the present invention.

The coding sequence may be operatively linked to an expression control sequence sufficient to drive expression. Recombinant DNA in accordance with the invention may be in the form of a vector. The vector may for example be a plasmid, cosmid or phage. A vector may include at least one selectable marker to enable selection of cells transfected (or transformed) with the vector. Such a marker or markers may enable selection of cells harbouring vectors incorporating heterologous DNA. The vector may contain appropriate start and stop signals. The vector may be an expression vector having regulatory sequences to drive expression. Vectors not having regulatory sequences may be used as cloning vectors (as may expression vectors).

Cloning vectors can be introduced into suitable hosts (for example *E. coli*) which facilitate their manipulation.

According to another aspect of the invention, there is therefore provided a host cell transfected or transformed with DNA according to the present invention. Such host cells may be prokaryotic or eukaryotic. Eukaryotic hosts may include yeasts, insect and mammalian cell lines. Expression hosts may be stably transformed. Unstable and cell-free expression systems may of course also be used.

DNA of the invention may also be in the form of a transgene construct designed for expression in a transgenic plant or animal. In principle, the invention is applicable to all animals, including birds such as placental mammals, (for example cattle, sheep, goats, water buffalo, camels and pigs), domestic fowl, amphibian species and fish species. The protein may be harvested from body fluids or other body products (such as eggs or milk, where appropriate). Such mammalian transgenic mammary expression systems are well known - see for example WO 88/00239, WO 90/05188 and WO 94/16570. The β-lactoglobulin promoter may be used in transgenic mammary expression systems.

Expression hosts, particularly transgenic animals, may contain other exogenous DNA to facilitate the expression, assembly, secretion and other aspects of the biosynthesis of molecules of the invention.

The invention is in principle capable of accommodating the use of synthetic DNA sequences, cDNAs, full genomic sequences and "minigenes", i.e. partial genomic sequences containing some, but not all, of the introns present in the full length gene.

DNA in accordance with the invention can in principle be prepared by any convenient method involving coupling together successive nucleotides, and/or ligating

oligo- and/or poly-nucleotides, including *in vitro* processes, as well as by the more usual recombinant DNA technology.

The invention will be further apparent from the following description, with reference to the several figures of the accompanying drawings, which show, by way of example only, forms of complement inhibition. Of the figures:

Figure 1 shows sequence alignments of the nucleotide sequences of four different types of rat factor H mRNA transcripts (rFH4.3, rFH2.7, rFH1.8 and rFH1.0; SEQ ID NOs: 1, 3, 4 and 2 respectively). Start and stop-codons are underlined, the polyadenylation initiation signal is written in italics;

Figure 2 shows a cofactor assay showing the functional activity of recombinant human FHp43. Lanes are as follows: Lane 1 - C3b with human Factor I (FI); lane 2 - C3b with rat FI; lane 3 - C3b with human FI and recombinant rat FHSCR1-7; lane 4 - C3b with human FI and recombinant human FHp43 (10 mM); and lane 5 - C3b with rat FI and purified human factor H; and

Figure 3 shows a cofactor assay showing the functional activity of recombinant rat FHSCR1-7. Lanes are as follows: Lane 1 - C3b with human FI; lane 2 - C3b with rat FI; lane 3 - C3b with human FI and recombinant human factor H; lane 4 - C3b with human FI and recombinant rat factor H; lane 5 - C3b with rat FI and recombinant rat FHSCR1-7; lane 6 - C3b with rat factor I and 10 mM recombinant rat FHSCR1-7; and lane 7 - C3b with human factor I and 10 mM recombinant FHp43.

Figure 4 shows the results of a cofactor assay performed to compare the functional activity of truncated recombinant human factor H SCR1-4, SCR1-5 and SCR1-6 with that of purified serum FHp155. The values given are arbitrary values representing the relative abundance of the 43 kDa C3b cleavage product obtained by the

factor I-mediated cleavage of ^{125}I-labelled C3b using densitometry. COncentration of purified recombinant and native factor H proteins added to the assay are given in the left column.

EXPERIMENTAL

With the following experiments, a truncated recombinant human and rat factor H are expressed in a high efficiency yeast expression system. The yield of expression is estimated to be in a range of up to 5mg of recombinant protein per litre of yeast culture.

Figures 2 and 3 show the results of the cofactor assays described below. The presence of an α' band at 43 kDa (a cleavage product of the α-chain of C3b) indicates cofactor activity (Figure 2, lane 4; Figure 3, lanes 3, 5, 6 and 7). Hence both the recombinant human FHp43 and rat FHSCR1-7 peptides cooperate with factor I in a species specific manner and, surprisingly, exhibit cofactor activity even at low concentrations (10 mM) when incubated with C3b and factor I of the corresponding species.

Materials and Methods

Isolation and characterization of 4 different factor H or factor H related gene products of the rat

Using a rat liver cDNA library in λ-ZAP II (#937506 STATAGENE, La Jolla, CA), cDNA clones rFH4.3, rFH1.8, rFH2.7 and rFH1.0 were isolated as follows. Approximately 300,000 colonies were screened with a 5' specific PstI/XhoI cDNA subfragment of the mouse factor H cDNA clone MH8 (Kirstensen, T. *et al.*, 1986, J. Immunol., 136: 3407). From eighteen hybridizing plaques obtained in the rescreen procedure, the four clones listed above were analysed further. The pBluescript SK- plasmid containing the cDNA insertions of interest were rescued from the λ-ZAP II phagemid by *in vivo* excision. The cDNA sequences of the 4 different types of clones was determined by sequencing both strands using the Sanger dideoxy chain termination method with Sequenase II (RTM) and the reagent kit (USB, Cleveland, USA).

RNA extraction and Northern blot analysis

Total RNA was isolated according to standard methods (Chirgwin, J.W. *et al.*, 1979, Biochemistry, 18: 5294), quantified by measuring the absorbence at 260 nm, separated on a formaldehyde-containing 1.2% agarose gel and blotted to Hybond N filters. Agarose gel electrophoresis, RNA transfer and hybridization of blots were performed by standard techniques (Sambrook, J., Frisch, E.F., and Maniatis, T.: Molecular cloning. A laboratory manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, New York, 1989). Northern blot filters were probed with a 5'-specific 553 bp long PstI/XhoI restriction subfragment of the murine factor H clone MH8 encoding SCR 1-2 of mouse factor H, and the 867 bp long cDNA insert of the rat specific factor H clone rFH1.0. The probes were used at a concentration of $5x10^6$ cpm of ^{32}P labelled cDNA/ml hybridization solution. Hybridization was performed at 65 °C in the absence of formamide. The washing of the Northern blots was carried out according to standard procedures (Sambrook et al., 1989, *supra*). The last washing step was performed in 0.3x SSC for 1 hour at 65 °C.

In order to obtain recombinant proteins of lower molecular weight than the naturally occuring factor H serum proteins and in order to opimise complement regulatory activity, we have modified the coding sequence of the human 1.8 kb factor H mRNA sequence. The modifications include a linker sequence insertion to enable an in frame cloning of the first codon for position 1 of the mature factor H protein with the coding sequence of the α-secretory factor contained in the yeast expression vector as well as the insertion of translation termination codons in order to obtain truncated forms of recombinant human factor H. Three constructs of different length were produced, encoding the SCR-motifs 1-4, SCR1-5, and SCR1-6. The pairs of oligonucleotide primers used to amplify the different stretches of coding sequence for human factor H (Schwaeble, W. *et al.*, 1987, Eur. J. Immunol., 17: 1485; Ripoche, J. *et al.*, 1988 Biochem. J., 249: 593; Schwaeble, W. *et al.*, 1991, Eur. J. Biochem., 198: 399-404; Estaller, C. *et al.*, Eur. J. Immunol., 21: 799) by PCR are listed below.

For the construct encoding SCR 1-4:

Forward primer (sense orientation)

3' gta **gaa ttc** GAA GAT TGCAAT GAA CTT 5' (SEQ ID NO: 5)

Reverse primer (ligates and introduces a stop codon at the end of the coding sequence for SCR4, anti-sense orientation)

3' AGA GGA TAT AGA GTC TTC TAA ACT **cgc cgg cgg** 5' (SEQ ID NO: 6)

For the construct encoding SCR 1-5:

Forward primer (sense orientation)

3' gta **gaa ttc** GAA GAT TGCAAT GAA CTT 5' (SEQ ID NO: 5)

Reverse primer (ligates and introduces a stop codon at the end of the coding sequence for SCR5, anti-sense orientation)

3' ATG AGT GGA AAT TCC TAA TTT ACT **cgc cgg cgg** 5' (SEQ ID NO: 7)

For the construct encoding SCR 1-6:

Forward primer (sense orientation)

3' gta **gaa ttc** GAA GAT TGCAAT GAA CTT 5' (SEQ ID NO: 5)

Reverse primer (ligates and introduces a stop codon at the end of the coding sequence for SCR6, anti-sense orientation)

3' GCA TCT GGT ATG AAA GGT CAT ACT **cgc cgg cgg** 5' (SEQ ID NO: 8)

Each of the three different PCR products was digested with the restriction endonucleases EcoRI and NotI and subcloned in the polylinker region of the EcoRI/ NotI digested yeast expression vector pPICZαA (Invitrogen BV, Leek, The Netherlands). Plasmids were grown in the E.coli strain TOP10F and sequenced to confirm the in frame cloning and the absence of cloning artifacts within the coding sequence. These constructs were used to transfect Pichia Pastoris host cells (strain SMD 1168) , transformants selected on YPD/Zeocin agar and genomic transmission of the constructs tested by PCR. Expression of the constructs was performed according to the manufacturer's protocol

The three different constructs therefore encode recombinant proteins representing different parts of the N-terminal sequence of human factor H

The protein sequence of the truncated recombinant human factor H protein SCR1-4 (a protein of 207 aa and 23 kDa) is SEQ ID NO: 9.

The protein sequence of the truncated recombinant human factor H protein SCR1-5 (a protein of 265 aa and 30 kDa) is SEQ ID NO: 10.

The protein sequence of the truncated recombinant human factor H protein SCR1-6 (a protein of 329 aa and 37 kDa) is SEQ ID NO: 11

In order to provide reagents that can be used to assess the therapeutic potential of recombinant factor H in rat experimental animal models, a truncated recombinant protein for rat factor H was prepared taking advantage of our rat factor H cDNA for FH4.3 (shown in figure 1 below):

As the functionally relevant SCR domains of rat factor H have not yet been mapped precisely, we expressed a slightly larger protein representing the 7 N-terminal SCR domains.

The following oligonucleotides were used to construct the cDNA encoding rat factor H SCR 1-7:

Forward primer (sense orientation)

3' gta **gaa ttc** GAA GAT TGT AAA GGT CCT CCT CC 5' (SEQ ID NO: 12)

Reverse primer (ligates and introduces a stop codon at the end of the coding sequence for SCR7, anti-sense orientation)

3' TTT ACG CAG GCA TAG TTC ATT **aga tct** cc 5' (SEQ ID NO: 13)

The PCR product was digested with the restriction endonucleases EcoRI and XbaI and subcloned in the polylinker region of the EcoRI/XbaI digested yeast expression vector pGAPZαA (Invitrogen BV, Leek, The Netherlands). Plasmids were grown in the E.coli strain TOP10F and sequenced to confirm the in frame cloning and the absence of cloning artifacts within the coding sequence. These constructs were used to transfect Pichia Pastoris host cells (strain SMD 1168) , transformants selected on YPD/Zeocin agar and genomic transmission of the constructs tested by PCR. Expression of the constructs was performed according to the manufacturer's protocol. After electroporation, Pichia pastoris cells were plated on MD plates (containing dextrose) and grown at 30 %C for 48 hours. Single colonies were picked from these plates and replated on Methanol containing MM plates (without dextrose) to select for AOX1- disrupted transformants which have the cDNA of interest inserted into the polylinker region. Alcohol oxidase genes AOX1 and AOX2 allow the metabolism of methanol, thereby providing a source of carbohydrates. MM plates (without dextrose) provide no other source of carbohydrates and so AOX1-disrupted transformants, which have a reduced ability to metabolise methanol, were recognised by their slower growth on dextrosol-free MM plates. The insertion of the cDNA construct of interest was further confirmed by PCR analysis of genomic DNA isolated from poorly growing colonies. In order to select for such colonies that secrete high rates of recombinant factor H, twenty AOX1-disrupted colonies were inoculated each in 10 ml of BMGY medium (Invitrogen) in a 50 ml tube and cultured at 30 °C with vigorous shaking (>200 rpm) for 48 hours to saturation (OD_{600} = 10.0-20.0). Cells were harvested by centrifugation for 10 minutes at room temperature at 4000 g, supernatant discarded and the pellet resuspended in 2 ml of BMMY (Invitrogen) medium. This time, tubes were only covered with two layers of sterile gauze and again, incubation occurred at 30°C with vigorous shaking (>200 rpm) for 48 hours. Cells were pelleted as before and supernatants analysed by Western blot analysis.

The protein sequence of the truncated recombinant rat factor H protein SCR1-7 (a protein of 428 aa and 49 kDa) is SEQ ID NO: 14

After induction of expression, supernatants from all of the 4 different constructs were run through an ion exchange column an the recombinant factor H proteins purified of Cl-4B sepharose coupled to polyclonal anti human or polyclonal anti-rat antibodies.

The recombinant truncated rat and human factor H proteins were assessed for complement regulatory activity and compared with purified serum factor H using a factor H dependent cofactor assay.

Cofactor assay

Functional activity of recombinant rat and human factor H was determined in a factor H dependent factor I mediated C3b cleavage assay. Therefore, human C3b and factor I were purified from peripheral blood as previously described (Misasi, R. et al., 1989, Eur. J. Immunol., 19: 1765). In order to establish a species-specific variant of this assay, rat factor I was purified from 2 ml of rat serum by fluid phase liquid chromatography using Pharmacia FPLC apparatus P500 and a Pharmacia Mono S HR 5/5 column eqilibrated with PE buffer at pH 6. Separation of serum proteins occurred by addition of PE-buffer plus 1M NaCl at pH 6 and a flow rate of 1 ml/min. Fractions were depleted of factor H by immune-chromatography using a Sepharose C14b column preabsorbed with the human anti-factor H monoclonal antibody OX23 (Schwaeble, W. et al., 1987, Eur. J. Immunol., 17: 1485). Human C3 and factor I were prepared from human serum as described earlier (Hammer, C.H.; Wirtz, G.H.; Renfer, L.; Gresham, H.D.; and Tack, B.F. J. Biol. Chem. 1981, 256: 3995 ; Lambris, J.D. ; Dobson, N.J.; and Ross, G.D. J.Exp.Med. 1980. 152: 1625. C3b was prepared by limited tryptic digestion of C3 (Bokisch V.A.; Müller-Eberhard, H.J.; and Cochrane, C.G. J.Exp.Med. 1969. 129: 1109) and consecutive chromatography on Sephadex G-100 (equilibrated in 10 mM sodium phosphate / 150 mM NaCl buffer, pH7.3) This preparation was radiolabelled with ^{125}I (1mCi037MBq of Na ^{125}I per 200 µg C3b) by the Iodogen method (Iodobeads purchased from Pierce Chemical Co. Rockford, IL) The specific activity was about 10^6 cpm /µg C3b. In the assay procedure 300 000 cpm of ^{125}I-labelled C3b was mixed with

increasing concentrations of recombinant human factor H proteins FH1-4, FH 1-5 and FH1-6 and serum factor H and 0.2 μg of purified human factor I in PBS containing 2 mM DFP in a total volume of 100μl and incubated for 30 minutes at 37°C. Cleavage of C3b was monitored by SDS-PAGE and autoradiography by the generation of the 73 kDa and 43 kDa cleavage products of the α-chain of C3b. Production of the 43 kDa cleavage product was indicative of cofactor activity.

Samples were analysed by SDS-PAGE under reducing conditions on a 9.5% SDS gel. Gels were dried and finally exposed to autoradiography on X-ray films.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: The University of Leicester
(B) STREET: University Road
(C) CITY: Leicester
(E) COUNTRY: United Kingdom
(F) POSTAL CODE (ZIP): LE1 7RH

(ii) TITLE OF INVENTION: Complement Inhibitor

(iii) NUMBER OF SEQUENCES: 14

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4229 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

TCGAGTCAAC TGCTCCCAGA TAGATCCAAG ACATGAGACT GTCAGCAAGA ATTATTTGGC 60

TTATATTATG GACTGTTTGT GTAGCAGAAG ATTGTAAAGG TCCTCCTCCA AGAGAAAATT 120

CAGAAATTCT CTCAGGTTCG TGGTCTGAAC AACTATATTC AGAAGGCACT CAGGCAACCT 180

ACAAATGCCG CCCTGGATAC CGAACACTTG GTACTATTGT AAAAGTATGC AAGAATGGAG 240

AATGGGTACC TTCTAACCCA TCAAGGATAT GTCGGAAAAG GCCATGTGGG CATCCCGGAG 300

ACACACCCTT TGGGTCCTTT AGGCTGGCAG TTGGATCTGA ATTTGAATTT GGTGCAAAGG 360

TTGTTTATAC ATGTGATGAA GGGTACCAAC TATTAGGTGA AATTGATTAC CGTGAATGTG 420

ATGCAGATGG GTGGACCAAT GATATTCCAA TATGTGAAGT TGTGAAGTGC TTGCCAGTGA 480

CAGAACTGGA GAATGGAAGA ATTGTGAGTG GTGCAGCCGA ACCAGACCAG GAATATTATT 540

TTGGACAGGT GGTACGCTTT GAATGCAACT CCGGCTTCAA GATTGAAGGA CAGAAAGAAA 600

TGCACTGCTC ATAAAATGGC CTCTGGAGCA ATGAAAAGCC ACAGTGTGTG GAAATTTCTT 660

GCCTGCCACC ACGAGTTGAA AATGGAGATG GTATATATCT GAAACCAGTT TACAAGGAGA 720

ATGAAAGATT CCAATATAAA TGTAAGCAAG GTTTTGTGTA CAAAGAAAGA GGGGATGCTG 780

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TCAGATATGA ATGTAAAAAT GGCTTCTATC CTGCAACCCG ATCACCTGTT TCAAAGTGTA 960

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TCAAACATGG ACGTCTGTAT TATGAAGAAA GCCGGAGACC CTACTTCCCA GTACCTATAG 1080

GAAAGGAGTA CAGCTATAAC TGTGACAACG GGTTTACAAC GCCTTCACAG TCATACTGGG 1140

ACTACCTTCG TTGCACAGTA AATGGGTGGG AGCCTGAAGT TCCATGCCTC AGGCAATGTA 1200

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GAATAATTAC TTGTCTTCAA GATGGATGGT CACCTCGACC CTCATGCATT AAGTCTTGTG 1560

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GCATTCCCCT GTTACACCAA GACTTAGTTG TTTTTCCCAG AGAAGTAAAA TACAAAGTTG 1800

GAGATTCGTT GAGTTTCTCT TGCCGTTCAG GACACAGAGT TGGAGCAGAT TTAGTGCAAT 1860

GCTACCACTT TGGATGGTCC CCTAATTTCC CAACGTGTGA AGGCCAAGTA AAATCATGTG 1920

ACCAACCTCT TGAAATCCCG AATGGGGAAA TAAAGGGAAC AAAAAAAGTT GAATACAGCC 1980

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CTCCCCCGCA GATTCCAAAT GCCCAAGTGA TTGAAACCAC CGTGAAATAC TTGGATGGAG 2520

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GTAAACATGG AAGGTGGCAG TCGTTACCAC GCTGCACGGA AAAAATTCCA TGTTCCCAGC 2640

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CTAAATATCC ATCTGGTGAC AAAGTACGTT ATGACTGTAA TAAACCTTTT GAATTATTTG 3300

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CAAATGTATA CAGCTAATTA CTGTGTCCTA CCTTTGTATC AATAAAGAAA TCTAAGAAAG 4200

TTCTTGCTTA AAAAAAAAAA AAAAAAAAA 4229

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 866 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

TCGAGTCAAC TGCTCCCAGA TAGATCCAAG ACATGAGACT GTCAGCAAGA ATTATTTGGC 60

TTATATTATG GACTGTTTGT GTAGCAGAAG ATTGTAAAGG TCCTCCTCCA AGAGAAAATT 120

CAGAAATTCT CTCAGGTTCG TGGTCTGAAC AACTATATTC AGAAGGCACT CAGGCAACCT 180

ACAAATGCCG CCCTGGATAC CGAACACTTG GTACTATTGT AAAAGTATGC AAGAATGGAG 240

AATGGGTACC TTCTAACCCA TCAAGGATAT GTCGGAAAAG GCCATGTGGG CATCCCGGAG 300

ACACACCCTT TGGGTCCTTT AGGCTGGCAG TTGGATCTGA ATTTGAATTT GGTGCAAAGG 360

TTGTTTATAC ATGTGATGAA GGGTACCAAC TATTAGGTGA AATTGATTAC CGTGAATGTG 420

ATGCAGATGG GTGGACCAAT GATATTCCAA TATGTGAAGT TGTGAAGTGC TTGCCAGTGA 480

CAGAACTGGA GAATGGAAGA ATTGTGAGTG GTGCAGCCGA ACCAGACCAG GAATATTATT 540

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TGCACTGCTC ATAAAATGGC CTCTGGAGCA ATGAAAAGCC ACAGTGTGTG GAAATTTCTT 660

GCCTGCCACC ACGAGTTGAA AATGGAGATG GATATAGAAA ATTCAGAGGA TCACCTCCGT 720

TTCGTACAAA GTGCATTGAG GGTCACATCA ATTATCCCAC TTGTGTATAA AATCGCTATA 780

CAATTATTAG TAAACCTTAT GGATGACACT TTGTTTAGAA ATGCACATGT ATATTACTAA 840

TACAGTTTGA ATTTACATTT GAAAAA 866

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2715 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

TCGAGTCAAC TGCTCCCAGA TAGATCCAAG ACATGAGACT GTCAGCAAGA ATTATTTGGC 60

TTATATTATG GACTGTTTGT GTAGCAGAAG ATTGTAAAGG TCCTCCTCCA AGAGAAAATT 120

CAGAAATTCT CTCAGGTTCG TGGTCTGAAC AACTATATTC AGAAGGCACT CAGGCAACCT 180

ACAAATGCCG CCCTGGATAC CGAACACTTG GTACTATTGT AAAAGTATGC AAGAATGGAG 240

AATGGGTACC TTCTAACCCA TCAAGGATAT GTCGGAAAAG GCCATGTGGG CATCCCGGAG 300

ACACACCCTT TGGGTCCTTT AGGCTGGCAG TTGGATCTGA ATTTGAATTT GGTGCAAAGG 360

TTGTTTATAC ATGTGATGAA GGGTACCAAC TATTAGGTGA AATTGATTAC CGTGAATGTG 420

ATGCAGATGG GTGGACCAAT GATATTCCAA TATGTGAAGT TGTGAAGTGC TTGCCAGTGA 480

CAGAACTGGA GAATGGAAGA ATTGTGAGTG GTGCAGCCGA ACCAGACCAG GAATATTATT 540

TTGGACAGGT GGTACGCTTT GAATGCAACT CCGGCTTCAA GATTGAAGGA CAGAAAGAAA 600

TGCACTGCTC ATAAAATGGC CTCTGGAGCA ATGAAAAGCC ACAGTGTGTG TTGAAACCTT 660

GTGATTTTCC ACAATTCAAA CATGGACGTC TGTATTATGA AGAAAGCCGG AGACCCTACT 720

TCCCAGTACC TATAGGAAAG GAGTACAGCT ATAACTGTGA CAACGGGTTT ACAACGCCTT 780

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GTCAAGATAC ATATTATTGT ACAGAGAATG GCTGGTCCCC TCCTCCCAAA TGCGTCCGTA 1020

TCAAGACTTG TTCAGTATCA GATATAGAAA TTGAAAATGG GTTTTTTTCT GAATCTGATT 1080

ATACATATGC TCTAAATAGA AAAACACGGT ATAGATGTAA ACAGGGATAT GTAACAAATA 1140

CCGGAGAAAT ATCAGGAATA ATTACTTGTC TTCAAGATGG ATGGTCACCT CGACCCTCAT 1200

GCATTAAGTC TTGTGATATG CCTGTATTTG AGAATTCTAT GACTAAGAAT AATAACACAT 1260

GGTTTAAACT CAATGACAAA TTAGACTATG AATGTCACAT TGGATATGAA AATGAATATA 1320

AACATACCAA AGGCTCTATA ACATGTACTT ATGATGGATG GTCTAGTACA CCCTCCTGTT 1380

ATGAAAGAGA ATGCAGCATT CCCCTGTTAC ACCAAGACTT AGTTGTTTTT CCCAGAGAAG 1440

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AGGGACCCAA TAAAATCCAG TGTGTTGACG GGAAGTGGAC AAGGTTGCCG ATATGCGTTG 1740

AGTATGAGAG AACATGTGGA GACCTTCCTG AACTTGAGCA TGGCTCTGTC AAGTTATCTG 1800

TCCCTCCCTA CCATCATGGA GATTCAGTGG AGTTCACTTG TACAGAAACC TTCACAATGA 1860

TTGGACATGC AGTAGTTTTC TGCATTAGTG GAAGGTGGAC CGAGCTTCCT CAATGTGTTG 1920

CAACAGATCA ACTGGAGAAG TGTAAAGCCC CGAAGTCAAC TGGCATAGAT GCAATTCATC 1980

CAAATAAGAA TGAATTTAAT CATAACTTTA GTGTGAGTTA CAGATGTAGA CAAAAGCAGG 2040

AGTATGAACA TTCAATCTGC ATCAATGGAA GATGGGATCC TGAACCAAAC TGTACAAGCA 2100

AAAGATTCTG CCCTCCTCCC CCGCAGATTC CAAATGCCCA AGTGATTGAA ACCACCGTGA 2160

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CAGAAGAAAT GGTGTGTAAA CATGGAAGGT GGCAGTCGTT ACCACGCTGC ACGGAAAAAA 2280

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CTGAAGGCTT TGGAATTGAT GGACCAGCAT TTATTAAATG TGTAGGAGGA CAGTGGTCTG 2640

AACCTCCCAA ATGCATAAAA ACTGATTGTG ACAACTTGCC CACATTTGAA ATTGCCAAAC 2700

CGACAGAAAA GAAAA 2715

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1532 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

TCGAGTCAAC TGCTCCCAGA TAGATCCAAG ACATGAGACT GTCAGCAAGA ATTATTTGGC 60

TTATATTATG GACTGTTTGT GTAGCAGAAG ATTGTAAAGG TCCTCCTCCA AGAGAAAATT 120

CAGAAATTCT CTCAGGTTCG TGGTCTGAAC AACTATATTC AGAAGGCACT CAGGCAACCT 180

ACAAATGCCG CCCTGGATAC CGAACACTTG GTACTATTGT AAAAGTATGC AAGAATGGAG 240

AATGGGTACC TTCTAACCCA TCAAGGATAT GTCGGAAAAG GCCATGTGGG CATCCCGGAG 300

ACACACCCTT TGGGTCCTTT AGGCTGGCAG TTGGATCTGA ATTTGAATTT GGTGCAAAGG 360

TTGTTTATAC ATGTGATGAA GGGTACCAAC TATTAGGTGA AATTGATTAC CGTTATCGAA 420

TGGATGGCTC TGACATTGTC ACATGTGTTA ATACGAAGTG GATTGGACAG CCGGTATGCA 480

AAGATAATTC CTGTGTGAAT CCACCACATG TGCCAAATGC TACTATACTA ACAAGGCACA 540

AGACTAAATA TCCATCTGGT GACAAAGTAC GTTATGACTG TAATAAACCT TTTGAATTAT 600

TTGGGGAAGT GGAAGTGATG TGCCAAAACG GGATTTGGAC AGAACCACCG AAATGCAAAG 660

ATTCAACAGG GAAATGTGGG CCTCCTCCAC CTATTGACAA TGGAGACATC ACCTCCTTGT 720

CATTACCAGT ATATGCACCA TTATCATCAG TTGAATATCA ATGCCAGAAC TATTATCTAC 780

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GATATAGAAA ATTCAGAGGA TCACCTCCGT TTCGTACAAA GTGCATTGAG GGTCACATCA 1020

ATTATCCCAC TTGTGTATAA AATCGCTATA CAATTATTAG TAAACCTTAT GGATGAGAAA 1080

TGCACATGTA TATTACTAAT ACAGTTTGAA TTTACATTTA AATATTGTTT AGCTCATTTC 1140

CTCTAATAAG TATATAAACT TTTTTTATAT GGTGGTTAAT CAGTAACTTT ACAGACTGTT 1200

GCCACAAAGC AAGAACATTA CATTCAAAAC TCCTAATCCA AATATGATAT GTCCAAGGAC 1260

AAACTATGTC TAAGCAAGAA AATAAATGTT AGTTCTTCAA TGTCTGTTTT TATTCAGGAC 1320

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CTGACTCTGA CTTCAAATTA GTATTACTTG CAATACATTA ACAACCAAAC TATCATAATA 1440

TCACAAATGT ATACAGCTAA TTACTGTGTC CTACCTTTGT ATCAATAAAG AAATCTAAGA 1500

AAGTTCTTGC TTAAAAAAAA AAAAAAAAAA AA 1532

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

TTCAAGTAAC GTTAGAAGCT TAAGATG 27

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

GGCGGCCGCT CAAATCTTCT GAGATATAGG AGA 33

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

GGCGGCCGCT CATTTAATCC TTAAAGGTGA GTA 33

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

GGCGGCCGCT CATACTGGAA AGTATGGTCT ACG 33

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 207 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Glu Asp Cys Asn Glu Leu Pro Pro Arg Arg Asn Thr Glu Ile Leu Thr
1 5 10 15

Gly Ser Trp Ser Asp Gln Thr Tyr Pro Glu Gly Thr Gln Ala Ile Tyr
20 25 30

```
Lys Cys Arg Pro Gly Tyr Arg Ser Leu Gly Asn Val Ile Met Val Cys
        35                  40                  45

Arg Lys Gly Glu Trp Val Ala Leu Asn Pro Leu Arg Lys Cys Gln Lys
    50                  55                  60

Arg Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly Thr Phe Thr Leu
65                  70                  75                  80

Thr Gly Gly Asn Val Phe Glu Tyr Gly Val Lys Ala Val Tyr Thr Cys
                85                  90                  95

Asn Glu Gly Tyr Gln Leu Leu Gly Glu Ile Asn Tyr Arg Glu Cys Asp
            100                 105                 110

Thr Asp Gly Trp Thr Asn Asp Ile Pro Ile Cys Glu Val Val Lys Cys
        115                 120                 125

Leu Pro Val Thr Ala Pro Glu Asn Gly Lys Ile Val Ser Ser Ala Met
    130                 135                 140

Glu Pro Asp Arg Glu Tyr His Phe Gly Gln Ala Val Arg Phe Val Cys
145                 150                 155                 160

Asn Ser Gly Tyr Lys Ile Glu Gly Asp Glu Glu Met His Cys Ser Asp
                165                 170                 175

Asp Gly Phe Trp Ser Lys Glu Lys Pro Lys Cys Val Glu Ile Ser Cys
            180                 185                 190

Lys Ser Pro Asp Val Ile Asn Gly Ser Pro Ile Ser Gln Lys Ile
        195                 200                 205
```

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 265 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

```
Glu Asp Cys Asn Glu Leu Pro Pro Arg Arg Asn Thr Glu Ile Leu Thr
1               5                   10                  15

Gly Ser Trp Ser Asp Gln Thr Tyr Pro Glu Gly Thr Gln Ala Ile Tyr
            20                  25                  30

Lys Cys Arg Pro Gly Tyr Arg Ser Leu Gly Asn Val Ile Met Val Cys
        35                  40                  45

Arg Lys Gly Glu Trp Val Ala Leu Asn Pro Leu Arg Lys Cys Gln Lys
    50                  55                  60
```

```
Arg Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly Thr Phe Thr Leu
65                  70                  75                  80

Thr Gly Gly Asn Val Phe Glu Tyr Gly Val Lys Ala Val Tyr Thr Cys
                85                  90                  95

Asn Glu Gly Tyr Gln Leu Leu Gly Glu Ile Asn Tyr Arg Glu Cys Asp
            100                 105                 110

Thr Asp Gly Trp Thr Asn Asp Ile Pro Ile Cys Glu Val Val Lys Cys
        115                 120                 125

Leu Pro Val Thr Ala Pro Glu Asn Gly Lys Ile Val Ser Ser Ala Met
    130                 135                 140

Glu Pro Asp Arg Glu Tyr His Phe Gly Gln Ala Val Arg Phe Val Cys
145                 150                 155                 160

Asn Ser Gly Tyr Lys Ile Glu Gly Asp Glu Glu Met His Cys Ser Asp
                165                 170                 175

Asp Gly Phe Trp Ser Lys Glu Lys Pro Lys Cys Val Glu Ile Ser Cys
            180                 185                 190

Lys Ser Pro Asp Val Ile Asn Gly Ser Pro Ile Ser Gln Lys Ile Ile
        195                 200                 205

Tyr Lys Glu Asn Glu Arg Phe Gln Tyr Lys Cys Asn Met Gly Tyr Glu
    210                 215                 220

Tyr Ser Glu Arg Gly Asp Ala Val Cys Thr Glu Ser Gly Trp Arg Pro
225                 230                 235                 240

Leu Pro Ser Cys Glu Glu Lys Ser Cys Asp Asn Pro Tyr Ile Pro Asn
                245                 250                 255

Gly Asp Tyr Ser Pro Leu Arg Ile Lys
            260                 265
```

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 329 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

```
Glu Asp Cys Asn Glu Leu Pro Pro Arg Arg Asn Thr Glu Ile Leu Thr
1               5                   10                  15

Gly Ser Trp Ser Asp Gln Thr Tyr Pro Glu Gly Thr Gln Ala Ile Tyr
            20                  25                  30
```

```
Lys Cys Arg Pro Gly Tyr Arg Ser Leu Gly Asn Val Ile Met Val Cys
          35                  40                  45

Arg Lys Gly Glu Trp Val Ala Leu Asn Pro Leu Arg Lys Cys Gln Lys
     50                  55                  60

Arg Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly Thr Phe Thr Leu
65                  70                  75                  80

Thr Gly Gly Asn Val Phe Glu Tyr Gly Val Lys Ala Val Tyr Thr Cys
                    85                  90                  95

Asn Glu Gly Tyr Gln Leu Leu Gly Glu Ile Asn Tyr Arg Glu Cys Asp
               100                 105                 110

Thr Asp Gly Trp Thr Asn Asp Ile Pro Ile Cys Glu Val Val Lys Cys
          115                 120                 125

Leu Pro Val Thr Ala Pro Glu Asn Gly Lys Ile Val Ser Ser Ala Met
     130                 135                 140

Glu Pro Asp Arg Glu Tyr His Phe Gly Gln Ala Val Arg Phe Val Cys
145                 150                 155                 160

Asn Ser Gly Tyr Lys Ile Glu Gly Asp Glu Glu Met His Cys Ser Asp
                    165                 170                 175

Asp Gly Phe Trp Ser Lys Glu Lys Pro Lys Cys Val Glu Ile Ser Cys
               180                 185                 190

Lys Ser Pro Asp Val Ile Asn Gly Ser Pro Ile Ser Gln Lys Ile Ile
          195                 200                 205

Tyr Lys Glu Asn Glu Arg Phe Gln Tyr Lys Cys Asn Met Gly Tyr Glu
     210                 215                 220

Tyr Ser Glu Arg Gly Asp Ala Val Cys Thr Glu Ser Gly Trp Arg Pro
225                 230                 235                 240

Leu Pro Ser Cys Glu Glu Lys Ser Cys Asp Asn Pro Tyr Ile Pro Asn
                    245                 250                 255

Gly Asp Tyr Ser Pro Leu Arg Ile Lys His Arg Thr Gly Asp Glu Ile
               260                 265                 270

Thr Tyr Gln Cys Arg Asn Gly Phe Tyr Pro Ala Thr Arg Gly Asn Thr
          275                 280                 285

Ala Lys Cys Thr Ser Thr Gly Trp Ile Pro Ala Pro Arg Cys Thr Leu
     290                 295                 300

Lys Pro Cys Asp Tyr Pro Asp Ile Lys His Gly Gly Leu Tyr His Glu
305                 310                 315                 320

Asn Met Arg Arg Pro Tyr Phe Pro Val
                    325
```

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

CCTCCTCCTG GAAATGTTAG AAGCTTAAGA TG 32

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

CCTCTAGATT ACTTGATACG GACGCATTT 29

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 428 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

```
Glu Asp Cys Lys Gly Pro Pro Pro Arg Glu Asn Ser Glu Ile Leu Ser
1               5                  10                  15

Gly Ser Trp Ser Glu Gln Leu Tyr Ser Glu Gly Thr Gln Ala Thr Tyr
            20                  25                  30

Lys Cys Arg Pro Gly Tyr Arg Thr Leu Gly Thr Ile Val Lys Val Cys
        35                  40                  45

Lys Asn Gly Glu Trp Val Pro Ser Asn Pro Ser Arg Ile Cys Arg Lys
    50                  55                  60

Arg Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly Ser Phe Arg Leu
65                  70                  75                  80

Ala Val Gly Ser Glu Phe Glu Phe Gly Ala Lys Val Val Tyr Thr Cys
                85                  90                  95

Asp Glu Gly Tyr Gln Leu Leu Gly Glu Ile Asp Tyr Arg Glu Cys Asp
```

```
                100                 105                 110

Ala Asp Gly Trp Thr Asn Asp Ile Pro Ile Cys Glu Val Val Lys Cys
        115                 120                 125

Leu Pro Val Thr Glu Leu Glu Asn Gly Arg Ile Val Ser Gly Ala Ala
    130                 135                 140

Glu Pro Asp Gln Glu Tyr Tyr Phe Gly Gln Val Val Arg Phe Glu Cys
145                 150                 155                 160

Asn Ser Gly Phe Lys Ile Glu Gly Gln Lys Glu Met His Cys Ser Glu
                165                 170                 175

Asn Gly Leu Trp Ser Asn Glu Lys Pro Gln Cys Val Glu Ile Ser Cys
            180                 185                 190

Leu Pro Pro Arg Val Glu Asn Gly Asp Gly Ile Tyr Leu Lys Pro Val
        195                 200                 205

Tyr Lys Glu Asn Glu Arg Phe Gln Tyr Lys Cys Lys Gln Gly Phe Val
    210                 215                 220

Tyr Lys Glu Arg Gly Asp Ala Val Cys Thr Gly Ser Gly Trp Asn Pro
225                 230                 235                 240

Gln Pro Ser Cys Glu Glu Met Thr Cys Leu Thr Pro Tyr Ile Pro Asn
                245                 250                 255

Gly Ile Tyr Thr Pro His Arg Ile Lys His Arg Ile Asp Asp Glu Ile
            260                 265                 270

Arg Tyr Glu Cys Lys Asn Gly Phe Tyr Pro Ala Thr Arg Ser Pro Val
        275                 280                 285

Ser Lys Cys Thr Ile Thr Gly Trp Ile Pro Ala Pro Arg Cys Ser Leu
    290                 295                 300

Lys Pro Cys Asp Phe Pro Gln Phe Lys His Gly Arg Leu Tyr Tyr Glu
305                 310                 315                 320

Glu Ser Arg Arg Pro Tyr Phe Pro Val Pro Ile Gly Lys Glu Tyr Ser
                325                 330                 335

Tyr Tyr Cys Asp Asn Gly Phe Thr Thr Pro Ser Gln Ser Tyr Trp Asp
            340                 345                 350

Tyr Leu Arg Cys Thr Val Asn Gly Trp Glu Pro Glu Val Pro Cys Leu
        355                 360                 365

Arg Gln Cys Ile Phe His Tyr Val Glu Tyr Gly Glu Ser Ser Tyr Trp
    370                 375                 380

Gln Arg Arg Tyr Ile Glu Gly Gln Ser Ala Lys Val Gln Cys His Ser
385                 390                 395                 400
```

Gly Tyr Ser Leu Pro Asn Gly Gln Asp Thr Tyr Tyr Cys Thr Glu Asn
405 410 415

Gly Trp Ser Pro Pro Pro Lys Cys Val Arg Ile Lys
420 425

CLAIMS

1. A molecule comprising at least complement control protein modules 1-4 of complement factor H, or a molecule resulting from partial modification thereof, or an allelic mutant thereof.

2. A molecule according to claim 1 comprising complement control protein modules 1-4, 1-5 or 1-6 of complement factor H, or a molecule resulting from partial modification thereof, or an allelic mutant thereof.

3. A molecule according to either one of claims 1 or 2, the complement factor H being human complement factor H.

4. A molecule according to claim 3, comprising complement control protein modules 1-4 and having the sequence of SEQ ID NO: 9.

5. A molecule according to claim 3, comprising complement control protein modules 1-5 and having the sequence of SEQ ID NO: 10.

6. A molecule according to claim 3, comprising complement control protein modules 1-6 and having the sequence of SEQ ID NO: 11.

7. A molecule according to either one of claims 1 or 2, the complement factor H being rat complement factor H.

8. A molecule according to claim 7, comprising complement control protein modules 1-7 and having the sequence of SEQ ID NO: 14.

9. A molecule according to any one of claims 1-8, for use in inhibiting complement activation.

10. A molecule according to claim 9, having an enhanced efficacy when compared to FHp155.

11. The use of a molecule according to any one of the preceding claims in the manufacture of a medicament for inhibiting complement activation.

12. A method of manufacture of a medicament for inhibiting complement activation, comprising the use of a molecule according to any one of claims 1-10.

13. A method of inhibiting complement activation comprising the use of a molecule according to any one of claims 1-10.

14. A nucleotide sequence having the formula of SEQ ID NO: 1 and encoding rat FH 4.3 kb mRNA.

15. A nucleotide sequence having the formula of SEQ ID NO: 2 and encoding rat FH 1.0 mRNA.

16. A DNA molecule comprising a sequence encoding a molecule according to any one of claims 1-10.

Figure 1

```
         10        20        30 -18    40        50        60
tcgagtcaactgctcccagatagatccaagacATGAGACTGTCAGCAAGAATTATTTGGC   rFH4.3
tcgagtcaactgctcccagatagatccaagacATGAGACTGTCAGCAAGAATTATTTGGC   rFH2.7
tcgagtcaactgctcccagatagatccaagacATGAGACTGTCAGCAAGAATTATTTGGC   rFH1.8
tcgagtcaactgctcccagatagatccaagacATGAGACTGTCAGCAAGAATTATTTGGC   rFH1.0

                              SCR1
         70        80       +1  90        100       110       120
TTATATTATGGACTGTTTGTGTAGCAGAAGATTGTAAAGGTCCTCCTCCAAGAGAAAATT   rFH4.3
TTATATTATGGACTGTTTGTGTAGCAGAAGATTGTAAAGGTCCTCCTCCAAGAGAAAATT   rFH2.7
TTATATTATGGACTGTTTGTGTAGCAGAAGATTGTAAAGGTCCTCCTCCAAGAGAAAATT   rFH1.8
TTATATTATGGACTGTTTGTGTAGCAGAAGATTGTAAAGGTCCTCCTCCAAGAGAAAATT   rFH1.0

         130       140       150       160       170       180
CAGAAATTCTCTCAGGTTCGTGGTCTGAACAACTATATTCAGAAGGCACTCAGGCAACCT   rFH4.3
CAGAAATTCTCTCAGGTTCGTGGTCTGAACAACTATATTCAGAAGGCACTCAGGCAACCT   rFH2.7
CAGAAATTCTCTCAGGTTCGTGGTCTGAACAACTATATTCAGAAGGCACTCAGGCAACCT   rFH1.8
CAGAAATTCTCTCAGGTTCGTGGTCTGAACAACTATATTCAGAAGGCACTCAGGCAACCT   rFH1.0

         190       200       210       220       230       240
ACAAATGCCGCCCTGGATACCGAACACTTGGTACTATTGTAAAAGTATGCAAGAATGGAG   rFH4.3
ACAAATGCCGCCCTGGATACCGAACACTTGGTACTATTGTAAAAGTATGCAAGAATGGAG   rFH2.7
ACAAATGCCGCCCTGGATACCGAACACTTGGTACTATTGTAAAAGTATGCAAGAATGGAG   rFH1.8
ACAAATGCCGCCCTGGATACCGAACACTTGGTACTATTGTAAAAGTATGCAAGAATGGAG   rFH1.0

                                     SCR2a
         250       260       270       280       290       300
AATGGGTACCTTCTAACCCATCAAGGATATGTCGGAAAAGGCCATGTGGGCATCCCGGAG   rFH4.3
AATGGGTACCTTCTAACCCATCAAGGATATGTCGGAAAAGGCCATGTGGGCATCCCGGAG   rFH2.7
AATGGGTACCTTCTAACCCATCAAGGATATGTCGGAAAAGGCCATGTGGGCATCCCGGAG   rFH1.8
AATGGGTACCTTCTAACCCATCAAGGATATGTCGGAAAAGGCCATGTGGGCATCCCGGAG   rFH1.0

         310       320       330       340       350       360
ACACACCCTTTGGGTCCTTTAGGCTGGCAGTTGGATCTGAATTTGAATTTGGTGCAAAGG   rFH4.3
ACACACCCTTTGGGTCCTTTAGGCTGGCAGTTGGATCTGAATTTGAATTTGGTGCAAAGG   rFH2.7
ACACACCCTTTGGGTCCTTTAGGCTGGCAGTTGGATCTGAATTTGAATTTGGTGCAAAGG   rFH1.8
ACACACCCTTTGGGTCCTTTAGGCTGGCAGTTGGATCTGAATTTGAATTTGGTGCAAAGG   rFH1.0
```

```
                    SCR2b
         370        380        390        400        410        420
TTGTTTATACATGTGATGAAGGGTACCAACTATTAGGTGAAATTGATTACCGTGAATGTG    rFH4.3
TTGTTTATACATGTGATGAAGGGTACCAACTATTAGGTGAAATTGATTACCGTGAATGTG    rFH2.7
TTGTTTATACATGTGATGAAGGGTACCAACTATTAGGTGAAATTGATTACCGT-------    rFH1.8
TTGTTTATACATGTGATGAAGGGTACCAACTATTAGGTGAAATTGATTACCGTGAATGTG    rFH1.0

                              SCR3
         430        440        450        460        470        480
ATGCAGATGGGTGGACCAATGATATTCCAATATGTGAAGTTGTGAAGTGCTTGCCAGTGA    rFH4.3
ATGCAGATGGGTGGACCAATGATATTCCAATATGTGAAGTTGTGAAGTGCTTGCCAGTGA    rFH2.7
------------------------------------------------------------    rFH1.8
ATGCAGATGGGTGGACCAATGATATTCCAATATGTGAAGTTGTGAAGTGCTTGCCAGTGA    rFH1.0


         490        500        510        520        530        540
CAGAACTGGAGAATGGAAGAATTGTGAGTGGTGCAGCCGAACCAGACCAGGAATATTATT    rFH4.3
CAGAACTGGAGAATGGAAGAATTGTGAGTGGTGCAGCCGAACCAGACCAGGAATATTATT    rFH2.7
------------------------------------------------------------    rFH1.8
CAGAACTGGAGAATGGAAGAATTGTGAGTGGTGCAGCCGAACCAGACCAGGAATATTATT    rFH1.0


         550        560        570        580        590        600
TTGGACAGGTGGTACGCTTTGAATGCAACTCCGGCTTCAAGATTGAAGGACAGAAAGAAA    rFH4.3
TTGGACAGGTGGTACGCTTTGAATGCAACTCCGGCTTCAAGATTGAAGGACAGAAAGAAA    rFH2.7
------------------------------------------------------------    rFH1.8
TTGGACAGGTGGTACGCTTTGAATGCAACTCCGGCTTCAAGATTGAAGGACAGAAAGAAA    rFH1.0


                                                   SCR4
         610        620        630        640        650        660
TGCACTGCTCATAAAATGGCCTCTGGAGCAATGAAAAGCCACAGTGTGTGGAAATTTCTT    rFH4.3
TGCACTGCTCATAAAATGGCCTCTGGAGCAATGAAAAGCCACAGTGTGTG----------    rFH2.7
------------------------------------------------------------    rFH1.8
TGCACTGCTCATAAAATGGCCTCTGGAGCAATGAAAAGCCACAGTGTGTGGAAATTTCTT    rFH1.0


         670        680        690        700        710        720
GCCTGCCACCACGAGTTGAAAATGGAGATGGTATATATCTGAAACCAGTTTACAAGGAGA    rFH4.3
------------------------------------------------------------    rFH2.7
------------------------------------------------------------    rFH1.8
GCCTGCCACCACGAGTTGAAAATGGAGAT------------------------------    rFH1.0
```

```
        730       740       750       760       770       780
ATGAAAGATTCCAATATAAATGTAAGCAAGGTTTTGTGTACAAAGAAAGAGGGGATGCTG   rFH4.3
------------------------------------------------------------   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

                                    SCR5
        790       800       810       820       830       840
TCTGCACGGGTTCTGGATGGAATCCTCAGCCTTCCTGTGAAGAAATGACATGTTTGACTC   rFH4.3
------------------------------------------------------------   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

        850       860       870       880       890       900
CATATATTCCAAATGGTATCTACACACCTCACAGGATTAAACACAGAATTGATGATGAAA   rFH4.3
------------------------------------------------------------   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

        910       920       930       940       950       960
TCAGATATGAATGTAAAAATGGCTTCTATCCTGCAACCCGATCACCTGTTTCAAAGTGTA   rFH4.3
------------------------------------------------------------   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

                                    SCR6
        970       980       990      1000      1010      1020
CAATTACTGGCTGGATCCCTGCTCCAAGATGTAGCTTGAAACCTTGTGATTTTCCACAAT   rFH4.3
----------------------------------TTGAAACCTTGTGATTTTCCACAAT   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

        1030      1040      1050      1060      1070      1080
TCAAACATGGACGTCTGTATTATGAAGAAAGCCGGAGACCCTACTTCCCAGTACCTATAG   rFH4.3
TCAAACATGGACGTCTGTATTATGAAGAAAGCCGGAGACCCTACTTCCCAGTACCTATAG   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0
```

```
        1090       1100       1110       1120       1130       1140
GAAAGGAGTACAGCTATAACTGTGACAACGGGTTTACAACGCCTTCACAGTCATACTGGG   rFH4.3
GAAAGGAGTACAGCTATAACTGTGACAACGGGTTTACAACGCCTTCACAGTCATACTGGG   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

                                                      SCR7
        1150       1160       1170       1180       1190       1200
ACTACCTTCGTTGCACAGTAAATGGGTGGGAGCCTGAAGTTCCATGCCTCAGGCAATGTA   rFH4.3
ACTACCTTCGTTGCACAGTAAATGGGTGGGAGCCTGAAGTTCCATGCCTCAGGCAATGTA   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

        1210       1220       1230       1240       1250       1260
TTTTCCATTATGTGGAATATGGAGAATCTTCATACTGGCAAAGAAGATATATAGAGGGTC   rFH4.3
TTTTCCATTATGTGGAATATGGAGAATCTTCATACTGGCAAAGAAGATATATAGAGGGTC   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

        1270       1280       1290       1300       1310       1320
AGTCTGCAAAAGTCCAGTGTCACAGTGGCTATAGTCTTCCAAATGGTCAAGATACATATT   rFH4.3
AGTCTGCAAAAGTCCAGTGTCACAGTGGCTATAGTCTTCCAAATGGTCAAGATACATATT   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

                                                      SCR8
        1330       1340       1350       1360       1370       1380
ATTGTACAGAGAATGGCTGGTCCCCTCCTCCCAAATGCGTCCGTATCAAGACTTGTTCAG   rFH4.3
ATTGTACAGAGAATGGCTGGTCCCCTCCTCCCAAATGCGTCCGTATCAAGACTTGTTCAG   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

        1390       1400       1410       1420       1430       1440
TATCAGATATAGAAATTGAAAATGGGTTTTTTTCTGAATCTGATTATACATATGCTCTAA   rFH4.3
TATCAGATATAGAAATTGAAAATGGGTTTTTTTCTGAATCTGATTATACATATGCTCTAA   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0
```

```
         1450       1460       1470       1480       1490       1500
ATAGAAAAACACGGTATAGATGTAAACAGGGATATGTAACAAATACCGGAGAAATATCAG    rFH4.3
ATAGAAAAACACGGTATAGATGTAAACAGGGATATGTAACAAATACCGGAGAAATATCAG    rFH2.7
------------------------------------------------------------    rFH1.8
                                                                rFH1.0

                                                        SCR9
         1510       1520       1530       1540       1550       1560
GAATAATTACTTGTCTTCAAGATGGATGGTCACCTCGACCCTCATGCATTAAGTCTTGTG    rFH4.3
GAATAATTACTTGTCTTCAAGATGGATGGTCACCTCGACCCTCATGCATTAAGTCTTGTG    rFH2.7
------------------------------------------------------------    rFH1.8
------------------------------------------------------------    rFH1.0

         1570       1580       1590       1600       1610       1620
ATATGCCTGTATTTGAGAATTCTATGACTAAGAATAATAACACATGGTTTAAACTCAATG    rFH4.3
ATATGCCTGTATTTGAGAATTCTATGACTAAGAATAATAACACATGGTTTAAACTCAATG    rFH2.7
------------------------------------------------------------    rFH1.8
------------------------------------------------------------    rFH1.0

         1630       1640       1650       1660       1670       1680
ACAAATTAGACTATGAATGTCACATTGGATATGAAAATGAATATAAACATACCAAAGGCT    rFH4.3
ACAAATTAGACTATGAATGTCACATTGGATATGAAAATGAATATAAACATACCAAAGGCT    rFH2.7
------------------------------------------------------------    rFH1.8
------------------------------------------------------------    rFH1.0

                                                        SCR10
         1690       1700       1710       1720       1730       1740
CTATAACATGTACTTATGATGGATGGTCTAGTACACCCTCCTGTTATGAAAGAGAATGCA    rFH4.3
CTATAACATGTACTTATGATGGATGGTCTAGTACACCCTCCTGTTATGAAAGAGAATGCA    rFH2.7
------------------------------------------------------------    rFH1.8
------------------------------------------------------------    rFH1.0

         1750       1760       1770       1780       1790       1800
GCATTCCCCTGTTACACCAAGACTTAGTTGTTTTTCCCAGAGAAGTAAAATACAAAGTTG    rFH4.3
GCATTCCCCTGTTACACCAAGACTTAGTTGTTTTTCCCAGAGAAGTAAAATACAAAGTTG    rFH2.7
------------------------------------------------------------    rFH1.8
------------------------------------------------------------    rFH1.0
```

```
               1810      1820      1830      1840      1850      1860
GAGATTCGTTGAGTTTCTCTTGCCGTTCAGGACACAGAGTTGGAGCAGATTTAGTGCAAT   rFH4.3
GAGATTCGTTGAGTTTCTCTTGCCGTTCAGGACACAGAGTTGGAGCAGATTTAGTGCAAT   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

                                                  SCR11
               1870      1880      1890      1900      1910      1920
GCTACCACTTTGGATGGTCCCCTAATTTCCCAACGTGTGAAGGCCAAGTAAAATCATGTG   rFH4.3
GCTACCACTTTGGATGGTCCCCTAATTTCCCAACGTGTGAAGGCCAAGTAAAATCATGTG   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

               1930      1940      1950      1960      1970      1980
ACCAACCTCTTGAAATCCCGAATGGGGAAATAAAGGGAACAAAAAAAGTTGAATACAGCC   rFH4.3
ACCAACCTCTTGAAATCCCGAATGGGGAAATAAAGGGAACAAAAAAAGTTGAATACAGCC   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

               1990      2000      2010      2020      2030      2040
ATGGTGACGTGGTGGAATATGATTGCAAACCTAGATTTCTACTGAAGGGACCCAATAAAA   rFH4.3
ATGGTGACGTGGTGGAATATGATTGCAAACCTAGATTTCTACTGAAGGGACCCAATAAAA   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

                                               SCR12
               2050      2060      2070      2080      2090      2100
TCCAGTGTGTTGACGGGAAGTGGACAAGGTTGCCGATATGCGTTGAGTATGAGAGAACAT   rFH4.3
TCCAGTGTGTTGACGGGAAGTGGACAAGGTTGCCGATATGCGTTGAGTATGAGAGAACAT   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

               2110      2120      2130      2140      2150      2160
GTGGAGACCTTCCTGAACTTGAGCATGGCTCTGTCAAGTTATCTGTCCCTCCCTACCATC   rFH4.3
GTGGAGACCTTCCTGAACTTGAGCATGGCTCTGTCAAGTTATCTGTCCCTCCCTACCATC   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0
```

```
        2170       2180       2190       2200       2210       2220
ATGGAGATTCAGTGGAGTTCACTTGTACAGAAACCTTCACAATGATTGGACATGCAGTAG   rFH4.3
ATGGAGATTCAGTGGAGTTCACTTGTACAGAAACCTTCACAATGATTGGACATGCAGTAG   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

                                                    SCR13
        2230       2240       2250       2260       2270       2280
TTTTCTGCATTAGTGGAAGGTGGACCGAGCTTCCTCAATGTGTTGCAACAGATCAACTGG   rFH4.3
TTTTCTGCATTAGTGGAAGGTGGACCGAGCTTCCTCAATGTGTTGCAACAGATCAACTGG   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

        2290       2300       2310       2320       2330       2340
AGAAGTGTAAAGCCCCGAAGTCAACTGGCATAGATGCAATTCATCCAAATAAGAATGAAT   rFH4.3
AGAAGTGTAAAGCCCCGAAGTCAACTGGCATAGATGCAATTCATCCAAATAAGAATGAAT   rFH2.7
------------------------------------------------------------   rFH1.8
                                                               rFH1.0

        2350       2360       2370       2380       2390       2400
TTAATCATAACTTTAGTGTGAGTTACAGATGTAGACAAAAGCAGGAGTATGAACATTCAA   rFH4.3
TTAATCATAACTTTAGTGTGAGTTACAGATGTAGACAAAAGCAGGAGTATGAACATTCAA   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

                                                    SCR14
        2410       2420       2430       2440       2450       2460
TCTGCATCAATGGAAGATGGGATCCTGAACCAAACTGTACAAGCAAAAGATTCTGCCCTC   rFH4.3
TCTGCATCAATGGAAGATGGGATCCTGAACCAAACTGTACAAGCAAAAGATTCTGCCCTC   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

        2470       2480       2490       2500       2510       2520
CTCCCCCGCAGATTCCAAATGCCCAAGTGATTGAAACCACCGTGAAATACTTGGATGGAG   rFH4.3
CTCCCCCGCAGATTCCAAATGCCCAAGTGATTGAAACCACCGTGAAATACTTGGATGGAG   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0
```

```
        2530       2540       2550       2560       2570       2580
AAAAAGTATCTGTTCTTTGCCAAGATGGTTACCTAACTCAGGGCCCAGAAGAAATGGTGT   rFH1.8
AAAAAGTATCTGTTCTTTGCCAAGATGGTTACCTAACTCAGGGCCCAGAAGAAATGGTGT   rFH2.7
------------------------------------------------------------   rFH4.3
------------------------------------------------------------   rFH1.0

                                        SCR15
        2590       2600       2610       2620       2630       2640
GTAAACATGGAAGGTGGCAGTCGTTACCACGCTGCACGGAAAAAATTCCATGTTCCCAGC   rFH4.3
GTAAACATGGAAGGTGGCAGTCGTTACCACGCTGCACGGAAAAAATTCCATGTTCCCAGC   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

        2650       2660       2670       2680       2690       2700
CCCCTAAAATTGAACATGGATCTATTAAGTCGCCCAGGTCCTCAGAAGAGAGGAGAGATT   rFH4.3
CCCCTAAAATTGAACATGGATCTATTAAGTCGCCCAGGTCCTCAGAAGAGAGGAGAGATT   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

        2710       2720       2730       2740       2750       2760
TAATTGAGTCCAGCAGTTATGAACACGGAACTACATTCAGCTATTGCTGTAGAGATGGAT   rFH4.3
TAATTGAGTCCAGCAGTTATGAACACGGAACTACATTCAGCTATTGCTGTAGAGATGGAT   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

        2770       2780       2790       2800       2810       2820
TCAAGATATCTGAAGAAAATAGGGTAACCTGCAACATGGGAAAATGGAGCTCTCTGCCTC   rFH4.3
TCAAGATATCTGAAGAAAATAGGGTAACCTGCAACATGGGAAAATGGAGCTCTCTGCCTC   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

        SCR16
        2830       2840       2850       2860       2870       2880
GTTGTGTTGGAATACCTTGTGGACCCCCACCTTCAATTCCTCTTGGTATTGTTTCTCATG   rFH4.3
GTTGTGTTGGAATACCTTGTGGACCCCCACCTTCAATTCCTCTTGGTATTGTTTCTCATG   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0
```

```
          2890       2900       2910       2920       2930       2940
AACTAGAAAGTTACCAATATGGAGAGGAGGTTACATACAATTGTTCTGAAGGCTTTGGAA   rFH4.3
AACTAGAAAGTTACCAATATGGAGAGGAGGTTACATACAATTGTTCTGAAGGCTTTGGAA   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

          2950       2960       2970       2980       2990       3000
TTGATGGACCAGCATTTATTAAATGTGTAGGAGGACAGTGGTCTGAACCTCCCAAATGCA   rFH4.3
TTGATGGACCAGCATTTATTAAATGTGTAGGAGGACAGTGGTCTGAACCTCCCAAATGCA   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

SCR17
          3010       3020       3030       3040       3050       3060
TAAAAACTGATTGTGACAACTTGCCCACATTTGAAATTGCCAAACCGACAGAAAAGAAAA   rFH4.3
TAAAAACTGATTGTGACAACTTGCCCACATTTGAAATTGCCAAACCGACAGAAAAGAAAA   rFH2.7
------------------------------------------------------------   rFH1.8
------------------------------------------------------------   rFH1.0

          3070       3080       3090       3100       3110       3120
AAAAATCATACAGGTCAGGAGAACAAGTGACATTCAGATGTCCACCTCCGTATCGAATGG   rFH4.3
------------------------------------------------------------   rFH2.7
----------------------------------------------------TATCGAATGG   rFH1.8
------------------------------------------------------------   rFH1.0

          3130       3140       3150       3160       3170       3180
ATGGCTCTGACATTGTCACATGTGTTAATACGAAGTGGATTGGACAGCCGGTATGCAAAG   rFH4.3
------------------------------------------------------------   rFH2.7
ATGGCTCTGACATTGTCACATGTGTTAATACGAAGTGGATTGGACAGCCGGTATGCAAAG   rFH1.8
------------------------------------------------------------   rFH1.0

SCR18
          3190       3200       3210       3220       3223       3240
ATAATTCCTGTGTGAATCCACCACATGTGCCAAATGCTACTATACTAACAAGGCACAAGA   rFH4.3
------------------------------------------------------------   rFH2.7
ATAATTCCTGTGTGAATCCACCACATGTGCCAAATGCTACTATACTAACAAGGCACAAGA   rFH1.8
------------------------------------------------------------   rFH1.0
```

```
               3250      3260      3270      3280      3290      3300
CTAAATATCCATCTGGTGACAAAGTACGTTATGACTGTAATAAACCTTTTGAATTATTTG  rFH4.3
------------------------------------------------------------  rFH2.7
CTAAATATCCATCTGGTGACAAAGTACGTTATGACTGTAATAAACCTTTTGAATTATTTG  rFH1.8
------------------------------------------------------------  rFH1.0

               3310      3320      3330      3340      3350      3360
GGGAAGTGGAAGTGATGTGCCAAAACGGGATTTGGACAGAACCACCGAAATGCAAAGATT  rFH4.3
------------------------------------------------------------  rFH2.7
GGGAAGTGGAAGTGATGTGCCAAAACGGGATTTGGACAGAACCACCGAAATGCAAAGATT  rFH1.8
------------------------------------------------------------  rFH1.0

SCR19
               3370      3380      3390      3400      3410      3420
CAACAGGGAAATGTGGGCCTCCTCCACCTATTGACAATGGAGACATCACCTCCTTGTCAT  rFH4.3
------------------------------------------------------------  rFH2.7
CAACAGGGAAATGTGGGCCTCCTCCACCTATTGACAATGGAGACATCACCTCCTTGTCAT  rFH1.8
------------------------------------------------------------  rFH1.0

               3430      3440      3450      3460      3470      3480
TACCAGTATATGCACCATTATCATCAGTTGAATATCAATGCCAGAACTATTATCTACTTA  rFH4.3
------------------------------------------------------------  rFH2.7
TACCAGTATATGCACCATTATCATCAGTTGAATATCAATGCCAGAACTATTATCTACTTA  rFH1.8
------------------------------------------------------------  rFH1.0

               3490      3500      3510      3520      3530      3540
AGGGAAATAAGATAGTAACATGTAGAAATGGAAAGTGGTCTCAGCCACCAACCTGCTTAC  rFH4.3
------------------------------------------------------------  rFH2.7
AGGGAAATAAGATAGTAACATGTAGAAATGGAAAGTGGTCTCAGCCACCAACCTGCTTAC  rFH1.8
------------------------------------------------------------  rFH1.0

SCR20
               3550      3560      3570      3580      3590      3600
ATGCATGTGTGATACCAGAAGATATTATGGAAAAACATAATATAGTTCTCAGATGGAGGG  rFH4.3
------------------------------------------------------------  rFH2.7
ATGCATGTGTGATACCAGAAGATATTATGGAAAAACATAATATAGTTCTCAGATGGAGGG  rFH1.8
------------------------------------------------------------  rFH1.0
```

```
         3610       3620       3630       3640       3650       3660
AAAATGCAAAGATTTATTCCCAATCAGGGGAGAATATTGAATTCATGTGTAAACCTGGAT   rFH4.3
------------------------------------------------------------   rFH2.7
AAAATGCAAAGATTTATTCCCAATCAGGGGAGAATATTGAATTCATGTGTAAACCTGGAT   rFH1.8
------------------------------------------------------------   rFH1.0
```

```
         3670       3680       3690       3700       3710       3720
ATAGAAAATTCAGAGGATCACCTCCGTTTCGTACAAAGTGCATTGAGGGTCACATCAATT   rFH4.3
------------------------------------------------------------   rFH2.7
ATAGAAAATTCAGAGGATCACCTCCGTTTCGTACAAAGTGCATTGAGGGTCACATCAATT   rFH1.8
ATAGAAAATTCAGAGGATCACCTCCGTTTCGTACAAAGTGCATTGAGGGTCACATCAATT   rFH1.0
```

```
         3730       3740       3750       3760       3770       3780
ATCCCACTTGTGTATAAaatcgctatacaattattagtaaaccttatggatgagaaatgc   rFH4.3
------------------------------------------------------------   rFH2.7
ATCCCACTTGTGTATAAaatcgctatacaattattagtaaaccttatggatgagaaatgc   rFH1.8
ATCCCACTTGTGTATAAaatcgctatacaattattagtaaaccttatggatgacactttg   rFH1.0
```

```
         3790       3800       3810       3820       3830       3840
acatgtatattactaatacagtttgaatttacatttaaatattgtttagctcatttcctc   rFH4.3
------------------------------------------------------------   rFH2.7
acatgtatattactaatacagtttgaatttacatttaaatattgtttagctcatttcctc   rFH1.8
tttagaaatgcacatgtatattactaatacagtttgaatttacatttgaaaaa-------   rFH1.0
```

```
         3850       3860       3870       3880       3890       3900
taataagtatataaacttttttttatatggtggttaatcagtaacttttacagactgttgcc   rFH4.3
------------------------------------------------------------   rFH2.7
taataagtatataaacttttttttatatggtggttaatcagtaacttttacagactgttgcc   rFH1.8
------------------------------------------------------------   rFH1.0
```

```
        3910       3920       3930       3940       3950       3960
acaaagcaagaacattacattcaaaactcctaatccaaatatgatatgtccaaggacaaa   rFH4.3
------------------------------------------------------------   rFH2.7
acaaagcaagaacattacattcaaaactcctaatccaaatatgatatgtccaaggacaaa   rFH1.8
------------------------------------------------------------   rFH1.0

        3970       3980       3990       4000       4010       4020
ctatgtctaagcaagaaaataaatgttagttcttcaatgtctgtttttattcaggacctt   rFH4.3
------------------------------------------------------------   rFH2.7
ctatgtctaagcaagaaaataaatgttagttcttcaatgtctgtttttattcaggacctt   rFH1.8
------------------------------------------------------------   rFH1.0

        4030       4040       4050       4060       4070       4080
tcagattttcttggatacctttgttaggttctgattcacagtgagtggaagacacactg   rFH4.3
------------------------------------------------------------   rFH2.7
tcagattttcttggatacctttgttaggttctgattcacagtgagtggaagacacactg   rFH1.8
------------------------------------------------------------   rFH1.0

        4090       4100       4110       4120       4130       4140
actctgacttcaaattagtattacttgcaatacattaacaaccaaactatcataatatca   rFH4.3
------------------------------------------------------------   rFH2.7
actctgacttcaaattagtattacttgcaatacattaacaaccaaactatcataatatca   rFH1.8
------------------------------------------------------------   rFH1.0

        4150       4160       4170       4180       4190       4200
caaatgtatacagctaattactgtgtcctacctttgtatcaataaagaaatctaagaaag   rFH4.3
------------------------------------------------------------   rFH2.7
caaatgtatacagctaattactgtgtcctacctttgtatcaataaagaaatctaagaaag   rFH1.8
------------------------------------------------------------   rFH1.0

        4210       4220       4230
ttcttgcttaaaaaaaaaaaaaaaaaaa                                   rFH4.3
---------------------------                                    rFH2.7
ttcttgcttaaaaaaaaaaaaaaaaaaa                                   rFH1.8
---------------------------                                    rFH1.0
```

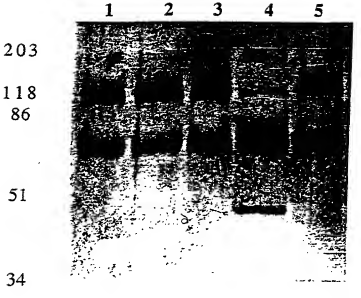

Figure 2

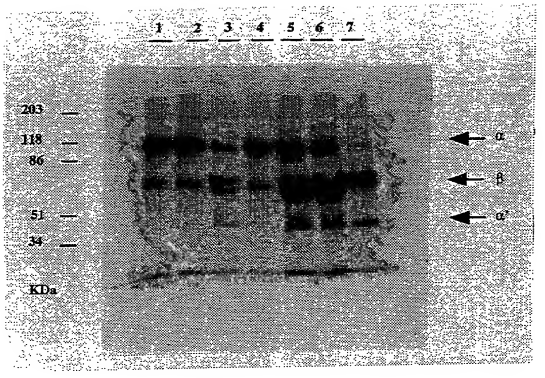

Figure 3

Figure 4

	FH SCR1-4	FH SCR1-5	FH SCR1-6	FHp155
10 nM	34 ± 2.3	36 ± 3.2	35 ± 1.3	1.6 ± 0.7
100 nM	144 ± 9	148 ± 7	156 ± 11	4.2 ± 1.6
200 nM	363 ± 14	374 ± 18	383 ± 11	7.8 ± 1.3